PATENT COOPERATION TREAT

| | From the INTERNATIONAL BUREAU |
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| PCT | То: |
| NOTIFICATION OF ELECTION (PCT Rule 61.2) Date of mailing (day/month/year) 02 May 2001 (02.05.01) | Commissioner US Department of Commerce United States Patent and Trademark Office, PCT 2011 South Clark Place Room CP2/5C24 Arlington, VA 22202 ETATS-UNIS D'AMERIQUE |
| | |
| International application No. PCT/GB00/02903 | Applicant's or agent's file reference PC/MG/P10870PC |
| International filing date (day/month/year) | Priority date (day/month/year) |
| 28 July 2000 (28.07.00) | 30 July 1999 (30.07.99) |
| Applicant | |
| MORRISON, James, Duncan et al | |
| | |
| in the demand filed with the International Preliminary I 22 February 200 in a notice effecting later election filed with the Interna | 01 (22.02.01) |
| 2. The election X was was was not was not made before the expiration of 19 months from the priority da Rule 32.2(b). | te or, where Rule 32 applies, within the time limit under |
| | |

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland

Authorized officer

Juan Cruz

Telephone No.: (41-22) 338.83.38

Facsimile No.: (41-22) 740.14.35



PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's | or ag | ent's file reference | | | See Notifica | ation of Transmittal of International |
|--|-----------------|--|---|--|-----------------|--|
| PC/MG/ | P108 | 70PC | FOR FURTHER ACTI | Preliminary Examination Report (Form PCT/IPEA/416) | | |
| Internation | al app | lication No. | International filing date (day) | /mont | vyear) | Priority date (day/month/year) |
| PCT/GB | 00/0 | 2903 | 28/07/2000 | | | 30/07/1999 |
| C07K14 | /595 | | national classification and IPC | GOV | v | |
| 1. This i | ntern s tran | ational preliminary exa smitted to the applican | arnination report has been pre at according to Article 36. | parec | l by this Inter | mational Preliminary Examining Authority |
| 2. This I | REPO | ORT consists of a total | of 5 sheets, including this co | ver sl | neet. | |
| (5 | een a see F | imended and are the b | pasis for this report and/or she 607 of the Administrative Ins | ets c | ontaining rec | , claims and/or drawings which have tifications made before this Authority a PCT). |
| | | | elating to the following items: | | | |
| 1 | | Basis of the report Priority | | | | |
| " | | <u>-</u> | opinion with regard to novelt | | | |
| íV | | Lack of unity of inven | | y, iriv | епиче ѕтер а | nd industrial applicability |
| V | ⊠ | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement | | | | |
| VI | | Certain documents c | ited | | | |
| VII | | Certain defects in the international application | | | | |
| VIII | ⊠ | Certain observations | on the international application | n . | | |
| Date of subi | nissio | n of the demand | Da | le of c | ompletion of th | is report |
| 22/02/2001 06.12. | | 12.20 | 01 | | | |
| lame and no reliminary | exami | address of the internationing authority: | nal Au | horize | d officer | SOM SCHES MICHELES |
| European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d | | | Pil 56 epmu d | at, D | | See The See Week of the See We |
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/02903

| | I. | Basis | of | the | report |
|--|----|-------|----|-----|--------|
|--|----|-------|----|-----|--------|

| 1. | the and | receiving Office in re | ents of the international application (Replacement sheets which have been furnished to esponse to an invitation under Article 14 are referred to in this report as "originally filed" this report since they do not contain amendments (Rules 70.16 and 70.17)): |
|----|--------------|--|--|
| | 1-2 | 2 | as originally filed |
| | Cla | ims, No.: | |
| | 1-2 | 3 : | as originally filed |
| 2. | lang | guage in which the in | Jage, all the elements marked above were available or furnished to this Authority in the iternational application was filed, unless otherwise indicated under this item. |
| | ine | ise elements were av | vailable or fumished to this Authority in the following language: , which is: |
| | | the language of a tr | ranslation furnished for the purposes of the international search (under Rule 23.1(b)). |
| | | the language of pub | plication of the international application (under Rule 48.3(b)). |
| | | the language of a tr 55.2 and/or 55.3). | ranslation furnished for the purposes of international preliminary examination (under Rule |
| 3. | Witl inte | n regard to any nucl or mational preliminary | eotide and/or amino acid sequence disclosed in the international application, the examination was carried out on the basis of the sequence listing: |
| | | contained in the inte | ernational application in written form. |
| | | filed together with th | ne international application in computer readable form. |
| | | furnished subseque | ently to this Authority in written form. |
| | | furnished subseque | ently to this Authority in computer readable form. |
| | | | the subsequently furnished written sequence listing does not go beyond the disclosure in plication as filed has been furnished. |
| | | The statement that listing has been furn | the information recorded in computer readable form is identical to the written sequence nished. |
| 4. | The | amendments have i | resulted in the cancellation of: |
| | | the description, | pages: |
| | | the claims, | Nos.: |
| | | the drawings, | sheets: |
| 5. | | | n established as if (some of) the amendments had not been made, since they have been eyond the disclosure as filed (Rule 70.2(c)): |



International application No. PCT/GB00/02903

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

- 6. Additional observations, if necessary:
- V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- 1. Statement

Novelty (N)

Yes:

Claims

No:

Claims 1-10,12,15,16,18-23

Inventive step (IS)

Yes: Claims

No: Clain

Claims 11,13,14,17

Industrial applicability (IA)

Yes:

Claims 1-23

No: Claims

2. Citations and explanations see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet





- 1. Reference is made to the following documents:
 - D1: US-A-5 446 026 (RUFF ET AL.) 29 August 1995 (1995-08-29)
 - D2: EP-A-0 417 725 (HOECHST AG) 20 March 1991 (1991-03-20) & US 5 646 272 A 8 July 1997 (1997-07-08) cited in the application
 - D3: P W SWAAN ET AL.: 'Enhanced transepithelial transport of peptides by conjugation to cholic acid' BIOCONJUGATE CHEMISTRY., vol. 8, no. 4, 1997, pages 520-525, XP002158726 AMERICAN CHEMICAL SOCIETY, WASHINGTON., US ISSN: 1043-1802
 - D4: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE. COLUMBUS, OHIO, US; STEPHAN, ZOUHAIR F. ET AL: 'Reduction of cardiovascular and thyroxine-suppressing activities of L-T3 by liver targeting with cholic acid' retrieved from STN Database accession no. 117:63425 CA XP002158727 cited in the application & BIOCHEM. PHARMACOL. (1992), 43(9), 1969-74, 1992,

Ad Section V: Reasoned statement under Rule 66.2(a)(ii); citations and explanations supporting such statement

- 2. Novelty (Article 33 (2) PCT)
- D1 discloses an amide of a bile salt selected from cholate, deoxycholate and 2.1 chenodeoxycholate wherein the group bound to the bile salt by the amide bond is a calcitonin decapeptide amide which was also identified as being an analgesic (see claims 1-7). D1 further discloses pharmaceutical compositions comprising this compound and their use for subcutaneous injection (see col.2 lines 35-54, claims 8-11). As a consequence, claims 1-10, 12, 15, 18-23 lack novelty.
- 2.2 D3 discloses that conjugation of peptides with cholic acid enhances transepithelial transport, ie. oral absorption (see Title). Several bile acid-peptide conjugates were tested, based on the general structural formula shown in Fig. 1, and the transport ability measured (see Table 1, Fig.2 and 3). The results show that this approach has the potential to increase intestinal absorption of otherwise poorly absorbed peptide molecules (see p.525 col.1 2§). Thus, D3 anticipates claims 1-10, 15, 16, 18-22.

3. Inventive step (Article 33 (3) PCT)

Dependent claims 11, 13-14, 17 do not appear to contain any additional features which, in combination with the features of the claims to which they refer, would render these claims inventive.

Ad Section VIII: Certain observations on the international application.

4. Clarity (Article 6 PCT)

Claim 18 lacks clarity, since the term "derivative" is vague and indefinite. The characteristic of being "physiologically functional" does not help to identify what is readily meant here. The applicant should define in the claim what is understood by said term.



(PCT Article 18 and Rules 43 and 44)

| Applicant's or agent's file reference | FOR FURTHER see Notification of | of Transmittal of International Search Report | | |
|---|--|---|--|--|
| PC/MG/P10870PC | ACTION (Form PCT/ISA/2 | (20) as well as, where applicable, item 5 below. | | |
| International application No. | International filing date (day/month/year) | (Earliest) Priority Date (day/month/year) | | |
| PCT/GB 00/02903 | 28/07/2000 | 30/07/1999 | | |
| Applicant | | A | | |
| THE UNIVERSITY COURT OF TI | HE UNIVERSITY OF GLASGOW | | | |
| according to Article 18. A copy is being tra | 2 | nority and is transmitted to the applicant | | |
| This International Search Report consists It is also accompanied by | of a total of3 sheets. a copy of each prior art document cited in this | report. | | |
| Basis of the report | | | | |
| With regard to the language, the i language in which it was filed, unle | nternational search was carried out on the basess otherwise indicated under this item. | sis of the international application in the | | |
| Authority (Rule 23.1(b)). | as carried out on the basis of a translation of th | | | |
| b. With regard to any nucleotide and was carried out on the basis of the | d/or amino acid sequence disclosed in the in sequence listing: | ternational application, the international search | | |
| | nal application in written form. | | | |
| filed together with the international application in computer readable form. | | | | |
| furnished subsequently to this Authority in written form. | | | | |
| furnished subsequently to this Authority in computer readble form. | | | | |
| the statement that the sub- international application as | the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished. | | | |
| the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished | | | | |
| | d unsearchable (See Box I). | | | |
| 3. Unity of invention is lacking (see Box II). | | | | |
| 4. With regard to the title , | | | | |
| the text is approved as sub | omitted by the applicant. | | | |
| X the text has been establish | ed by this Authority to read as follows: | | | |
| IMPROVEMENT OF PEPTIDE TRANSPORT BY CONJUGATION WITH BILE ACIDS | | | | |
| 5. With regard to the abstract, | | | | |
| X the text is approved as submitted by the applicant. | | | | |
| the text is approved as submitted by the applicant. the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority. | | | | |
| 6. The figure of the drawings to be publis | shed with the abstract is Figure No. | | | |
| as suggested by the applic | | None of the figures. | | |
| because the applicant failed to suggest a figure. | | | | |
| because this figure better characterizes the invention. | | | | |

International Application No POBB 00/02903

A. CLASSIFICATION OF SUBJECT MATTERIES IPC 7 C07K14/595 C07K14/575

C07K14/47

A61K47/48

A61K38/04

| According t | o International Patent Classification (IPC) or to both national classification and IPC | |
|-------------|---|-----------------------|
| B. FIELDS | SEARCHED | |
| | ocumentation searched (classification system followed by classification symbols) C07K A61K | |
| Documenta | tion searched other than minimum documentation to the extent that such documents are included in the | he fields searched |
| Electronic | lata base consulted during the international search (name of data base and, where practical, search t | erms used) |
| CHEM A | BS Data, WPI Data | |
| C. DOCUM | ENTS CONSIDERED TO BE RELEVANT | |
| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| Х | US 5 446 026 A (RUFF ET AL.) 29 August 1995 (1995-08-29) claim 1 | 1-10,12, 15-23 |
| X | P W SWAAN ET AL.: "Enhanced transepithelial transport of peptides by conjugation to cholic acid" BIOCONJUGATE CHEMISTRY., vol. 8, no. 4, 1997, pages 520-525, XP002158726 AMERICAN CHEMICAL SOCIETY, WASHINGTON., US ISSN: 1043-1802 the whole document | 1-10, 15-23 |

| X Further documents are listed in the continuation of box C. | Patent family members are listed in annex. |
|---|---|
| Special categories of cited documents: 'A' document defining the general state of the art which is not considered to be of particular relevance 'E' earlier document but published on or after the international filing date 'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) 'O' document referring to an oral disclosure, use, exhibition or other means 'P' document published prior to the international filing date but later than the priority date claimed | 'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention 'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone 'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents such combination being obvious to a person skilled in the art '&' document member of the same patent family |
| Date of the actual completion of the international search | Date of mailing of the international search report |
| 30 January 2001 | 14/02/2001 |
| Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl. Fax: (+31-70) 340-3016 | Authorized officer Masturzo, P |

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P(8 00/02903

| C.(Continua | tion) DOCUMENTS CONSIDER BE RELEVANT | |
|-------------|--|-----------------------|
| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| A | EP 0 417 725 A (HOECHST AG) 20 March 1991 (1991-03-20) the whole document & US 5 646 272 A 8 July 1997 (1997-07-08) cited in the application | 1-23 |
| A | Cited in the application DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; STEPHAN, ZOUHAIR F. ET AL: "Reduction of cardiovascular and thyroxine-suppressing activities of L-T3 by liver targeting with cholic acid" retrieved from STN Database accession no. 117:63425 CA XP002158727 cited in the application & BIOCHEM. PHARMACOL. (1992), 43(9), 1969-74, 1992, abstract | 1-23 |

Information on patent family members

International Application No
PC 3 00/02903
ily Publication

| | Patent documer cited in search rep | | Publication date | | Patent family member(s) | Publication date |
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| | EP 417725 | Α | 20-03-1991 | DE | 3930696 A | 28-03-1991 |
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| | | | | US | 5462933 A | 31-10-1995 |
| | | | | US | 5668126 A | 16-09-1997 |
| | | | | US | 5646272 A | 08-07-1997 |
| | | | | ZA | 9007300 A | 26-06-1991 |
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REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

| For receiving Office use only |
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| International Application No. |
| International Filing Date |
| Name of receiving Office and "PCT International Application" |
| Applicant's or agent's file reference |

| | Applicant's or agent's file reference (if desired) (12 characters maximum) PC/MG/P10870PC |
|--|--|
| Box No. I TITLE OF INVENTION | |
| PEPTIDE TRANSPORT | |
| Box No. II APPLICANT | |
| Name and address: (Family name followed by given name: for a designation. The address must include postal code and name of cou address indicated in this Box is the applicant's State (that is, country, of residence is indicated below.) | |
| THE UNIVERSITY COURT OF THE UNIVOF GLASGOW No.10 THE SQUARE | /ERSITY Facsimile No. |
| UNIVERSITY AVENUE | Table |
| GLASGOW G12 8QQ United Kingdom | Teleprinter No. |
| State (that is, country) of nationality: GB | State (that is, country) of residence: GB |
| This person is applicant for the purposes of: All designated X all designated the United States | States except atte United States the States indicated in the States of America only the Supplemental Box |
| Box No. III FURTHER APPLICANT(S) AND/OR (FURTI | IER) INVENTOR(S) |
| Name and address: (Family name followed by given name; for a ladesignation. The address must include postal code and name of cour address indicated in this Box is the applicant's State (that is, country) of residence is indicated below.) MORRISON James Duncan West Medical Building University of Glasgow University Avenue GLASCOW G12 800 United Kingdo State (that is, country) of nationality: GB | applicant only X applicant and inventor inventor only (If this check-box is marked, do not fill in below.) |
| This person is applicant all designated all designated for the purposes of: | States except ates of America |
| Further applicants and/or (further) inventors are indicated or | a continuation sheet. |
| Box No. IV AGENT OR COMMON REPRESENTATIVE: | OR ADDRESS FOR CORRESPONDENCE |
| The person identified below is hereby/has been appointed to act or of the applicant(s) before the competent International Authorities a | behalf agent common representative |
| Name and address: McCALLUM, William Potter; MacDOUGALL, Do Tymoteusz; NAISMITH, Robert Stewart; HORN | |

Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Andrew; NEWELL, Campbell; KERR, Sheila Agnes Fife; MORELAND, David;

CRUIKSHANK & FAIRWEATHER, 19 ROYAL EXCHANGE SQUARE,

GLASGOW G1 3AE, UNITED KINGDOM (GB)

Form PCT/RO/101 (first sheet) (July 1998; reprint January 2000)

GODWIN, Edgar James;

See Notes to the request form

Facsimile No.

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| | Sheet No2 |
|---|--|
| Continuation of Box No. III FUER APPL | LICANT(S) AND/OR (FURTHER) IN OR(S) |
| | ces is used, this sheet should not be included in the request. |
| Name and address: (Family name followed by given designation. The address must include postal code and address indicated in this Box is the applicant's State (Not of residence is indicated below.) LUCAS Michael Leslie West Medical Building University of Glasgow University Avenue GLASGOW G12 8QQ United Kingdom | name: for a legal entity, full official d name of country. The country of the hat is, country) of residence if no State This person is: applicant only X applicant and inventor inventor only (If this check-hox is marked, do not fill in below.) |
| State (that is, country) of nationality: GB | State (that is, country) of residence: GB |
| This person is applicant all designated for the purposes of: | all designated States except the United States of America only the States indicated in the Supplemental Box |
| Name and address: (Family name followed by given n designation. The address must include postal code and address indicated in this Box is the applicant's State (the of residence is indicated below.) WHEELER Sarah West Medical Building University of Glasgow University Avenue GLASGOW G12 8QQ United Kingdom | This person is: applicant only applicant and inventor inventor only (If this check-box is marked, do not fill in below.) |
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Further applicants and/or (further) inventors are indicated on another continuation sheet.

| В | ox N | Vo.V | DESIGNATION OF ST | s | | | | | | | | | | |
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| T | e fo | ollowing | designations are hereby made | e under Rule 4 9(a |) (m | ark tha | analizable shock have all | | | | | | | |
| The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked): Regional Patent | | | | | | | | | | | | | | |
| AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT | | | | | | | | | | | | | | |
| [2] | EA | EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT | | | | | | | | | | | | |
| LA | EP | FD Furgness Potents AT Austria DE Dalaisse CVI and VII a | | | | | | | | | | | | |
| 1 | | MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent | | | | | | | | | | | | |
| I I X | OA | OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any specify on dotted line) Specify on dotted line) | | | | | | | | | | | | |
| Nat | National Patent (if other kind of protection or treatment desired, specify on dotted line): | | | | | | | | | | | | | |
| | X AE United Arab Emirates | | | | | | | | | | | | | |
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(54) Title: PEPTIDE TRANSPORT

(57) Abstract: The present invention relates to improving and/or increasing the bioavailability of a biologically active substance, such as a peptide. In particular the present invention relates to the conjugation of the biologically active substance to a bile acid. The conjugated biologically active substance is suitable particularly for oral or parental administration.